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10/722,695	11/24/2003	Joseph L. Wooters	22058-536 (AM101268)	8353

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EXAMINER	
ARCHIE, NINA	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,695	WOOTERS ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-61* is/are pending in the application.

4a) Of the above claim(s) *45-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed 6/20/2007. Claim 38 has been amended. Claims 38-61 are currently pending. Claims 45-61 have been withdrawn from consideration. Claims 1-37 and 62-67 have been cancelled.

Rejections Withdrawn

2. In view of the Applicant's amendment and remark following rejections are withdrawn.

a) Rejection of claim 38 under 35 U.S.C. 112, second paragraph, page 8 last paragraph is withdrawn in light of in light of applicant's amendment thereto.

Claim Rejections Maintained- 35 USC § 112

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 38-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant arguments:

A) Applicants' assertion to satisfy the enablement requirement, the specification need only teach one skilled in the art how to make and use the invention as claimed (without undue experimentation). Applicants' assertion that in order to establish a prima facie case of non-enablement, the examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re Wright, 999 F.2d 1557, 1561-562, 27 USPQ2d 151 O, 1513 (Fed. Cir. 1993). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement. In re Morehouse, 545 F.2d 162, 165, 192 USPQ 29, 32 (CCPA 1976). Further, even a broad allegation that the disclosure is speculative, coupled with a recitation of various difficulties, which might be encountered in practice, is not sufficient basis for requiring proof of operability. In re Chilowsky, 229 F.2d 457, 462, 108 USPQ 321,325 (CCPA 1956). In the present case, Applicants respectfully submit that the examiner has not provided acceptable evidence that the claimed invention is inconsistent with enablement. At best, the examiner has made broad allegations that the disclosure is speculative and recited various difficulties, which might be encountered in practice of the invention. This is not a sufficient evidentiary basis for requiring proof of enablement and a shifting of the burden of proof to appellant.

Applicants' assertion that contrary to the examiner's contention, the specification provides guidance to one of ordinary skill in the art as to how to determine what therapeutic agents would be useful in the recited method without undue experimentation. The present inventors have discovered that the mechanism for Chlamydia infection may be mediated through a cyclophilin pathway. Indeed, Example 5 of the specification shows that antibodies to cyclophilin blocks Chlamydia infection of human cells thereby demonstrating that disruption of cyclophilin mediated pathways is important to inhibiting Chlamydia infection. Thus, it would reasonably appear that one of skill in the art could reasonably expected inhibitors of cyclophilin binding to be useful in the treatment of Chlamydia infection. In this regard, the following passage from PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) is instructive here.

In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (1982).

In the present case, even if a considerable amount of experimentation is required to determine which cyclophilin inhibitors are effective in blocking Chlamydia

infection, such experimentation is routine to those of ordinary skill in the relevant art. Indeed, the specification discloses assays that may be performed to determine if the inhibitor is capable of blocking the interaction between cylcophilin and a cyclophylin binding partner. This includes the assay disclosed in Example 5 that may be used to directly screen agents that block the Chlamydia infection in human cells.
Further, the possibility for inoperable embodiments within the scope of the claims is not a sufficient factor for nonenablement, as it is not a function of the claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974). The Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples set forth in the specification. Texas Instruments v. U.S. Int'l Trade Comm., 805 F.2d 1558, 1562, 231 USPQ 833,835 (Fed. Cir 1986). Accordingly, Applicants respectfully submit that the examiner has not met the burden of proof by advancing acceptable reasoning inconsistent with enablement.

Examiner's Response to Applicant's Arguments:

Examiner accepts that claim 38 has been amended. Examiner accepts that Example 5 of the specification shows that antibodies to cyclophilin blocks Chlamydia infection of human cells thereby demonstrating that disruption of cyclophilin mediated pathways is important to inhibiting Chlamydia infection which is an in vitro method that would expect inhibitors of cyclophilin binding to be useful in the treatment of Chlamydia infection. However Applicant has not shown an in vivo method that would expect inhibitors of cyclophilin binding to be useful in the treatment of Chlamydia infection.

Examiner accepts that the specification discloses assays that may be performed to determine if the inhibitor is capable of blocking the interaction between cylcophilin and a cyclophylin binding partner, which includes the assay disclosed in Example 5 that may be used to directly screen agents that block the Chlamydia infection in human cells. However the Examiner disagrees with the Applicants' assertions as discussed

above that one skilled in the art could readily make and use the claimed method without undue experimentation because there is no correlation between in vivo and vitro example of a method of method of treating a Chlamydia infection in a subject.

4. As outlined previously, the instant claims are to drawn to a method of treating a Chlamydia infection in a subject.

The specification is not enabled for any method for treating a Chlamydia infection in a subject, the method comprising administering to a subject in need thereof an effective amount of a therapeutic agent that disrupts the interaction between cyclophilin and a cyclophilin binding partner.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims. The claim is very broad and the therapeutic agent being used to administer to a subject is directed to all antibodies with specificity to cyclophilin A. Furthermore the claims are drawn to a method of treating a Chlamydia infection.

Therefore it is hard for one skilled in the art to determine if all antibodies specific for cyclophilin A can be used in treating a Chlamydia infection in a subject. The quantity of experimentation required to practice the invention as claimed would require in vivo and in vitro studies of the antibody that is specific for cyclophilin A, the detection antibodies each specific for an epitope which induce an immune response, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of Chlamydia infection comprising administering a therapeutic agent which is an antibody specific for cyclophilin A to a subject and since determination of these factors for a particular antibody for the particularly claimed conditions, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Nature of the invention. The claims are drawn to methods for treating a Chlamydia infection in a subject, comprising administering to a subject in need thereof an effective therapeutic agent amount of a therapeutic agent that disrupts the interaction between cyclophilin and a cyclophilin binding partner.

The specification discloses in Example 1 (see pp. 32-33), the presence of cyclophilin A in the elementary bodies of C. *pneumoniae* and C. *trachomatis*. Example 2 and 4 (see pg. 32-33) discloses the binding affinities the cyclophilin-binding polypeptides to magnetic beads coated with cyclophilin A and binding of some recombinant Chlamydia proteins to the cyclophilin A immobilized on a substrate. Example 3 (see pg. 33) discloses crosslinking complexes of cyclophilin A and one or more Chlamydia protein. Example 5 (see pg. 33) discloses limited in vitro data that demonstrate the ability of anti-cyclophilin A antibodies to block Chlamydia infection of human cells.

The state of the prior art. The state of the art indicate that Chlamydia have a complex life cycle and that elementary bodies enters into the cell by mechanisms unknown, and also through unknown signals, whereby reticulate bodies reconvert to elementary bodies (see Engel 2004 National Academy of the Sciences of USA Vol. 101, No. 27

pgs. 9947-9948 in its entirety). The state of the art indicate that "to be an effective treatment for a Chlamydia infection, an antimicrobial agent must penetrate four membrane layers: (1) the host cell plasma membrane; (2) the inclusion membrane; (3) the Chlamydia outer membrane; and (4) the Chlamydia cytoplasmic membrane" (see Schaechter et al 1999 Mechanisms of Microbial Diseases Third Edition pgs. 266 column 1). The state of the shows an in vitro and in vivo study of administering 2 different monoclonal antibodies (anti-L3T4+ and anti-Lyt-2+). The treatment with anti-L3T4 in vivo and in vitro had no effect on protection of Chlamydia. However the anti-Lyt-2 monoclonal dramatically reduced infection in vivo, however in vitro, the complement was necessary to observe the effect, since the treatment of primed cells with anti-Lyt-2 monoclonal antibody alone was not able to abrogate protection (see Gatel et al 1992 Immunology Vol. 77 pgs. 284-288 especially abstract and pg. 286). The state of the art show that monoclonal antibodies recognizing MOMP (major outer membrane protein) specific epitopes were shown to passively transfer immunity to mice infected with *C. muridarum* in a mouse model for human genital tract infection and also to protect mice pregnant mice from *C. abortus*-induced abortion (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract see pg. 267 column 1 paragraph 2). The state of the show that monoclonal antibodies show that recognize monoclonal antibodies neutralized the infectivity of serovar B in an animal, suggesting a functional relationship between antibody-mediated protection of an animal toxicity and chlamydial infectivity (Zhang et al 1989 Infection and Immunity Vol. 57 No. 2 pgs. 636-638 in its entirety).

The state of the art indicates that Chlamdyia *trachomatis* have a MIP (macrophage infectivity potentiator) gene that is located in both elementary and reticulate bodies. Furthermore it is noted that the MIP gene of *Chlamydia trachomatis* show strong homology with MIP gene of surface exposed *Legionella pneumophila.* However there are no surface exposed epitopes of the *Chlamdyia trachomatis* detected therefore it is unlikely that the MIP like protein of *Chlamdyia trachomatis* is surface exposed and specific antibodies of the MIP like protein of Chlamdyia *trachomatis* are nonneutralizing (see Lundemose et al. 1992 Mol Microbiol. Vol. 6 Issue 17 pgs. 2539-2540). Furthermore the state of the art also show that the

Chlamdyia trachomatis MIP like protein possess peptidyl-prolyl cis-trans isomerases activity (see Lundesome et al 1993 Journal of Bateriology pg. 3669 column 1) which is identical to cyclophilin including cyclophilin A (see Mann 2001 Natl. Prod. Rep. Vol. 18 pg. 418 column 2 paragraph 1). The art has not shown any antibodies that are specific for cyclophilin A to target cells infected with Chlamydia. The state of the art has not shown any cell surface receptors for Chlamydia that would bind to cyclophilin A. Therefore the art is unpredictable to antibodies that can bind to cyclophilin A and thus target cells infected with Chlamydia which have a complex life cycle.

The state of the art does show immunization with cyclophilin A that inhibits HIV-1 infection, which suggest the possibility that HIV-1 infection could be inhibited by antibodies. The state of the art teaches that cyclophilin A has chemotactic activity and that that the body produces cyclophilin A in response to HIV-1 infection. The art shows that cyclophilin A are recognized by cell surface receptors CD147 on CD4+Tcells (Sherry et al 1998 Proc. Natl. Acad. Sci. USA Vol. 95 pgs. 1758-1763 in its entirety). Therefore the art questions if cyclophilin A is produced in response to a Chlamydia infection how can Chlamydia be treated by an antibody that is specific for cyclophilin A.

The state of the art indicates that the best approach for controlling the spread of chlamydial infections, in animal and human populations are DNA vaccination (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract). The state of the art indicates that vaccination approaches have proved unsuccessful in combating human chlamydial infections (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract, pg. 265 column 2 paragraphs 2-4, pg. 266 column 1 paragraph 1). The art shows that if detected early, chlamydial infections are treatable with antibacterial agents (Igietseme et al 2003 Expert Rev. Vaccines Vol. 2 No. 1 see pg. 130). The art discloses defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not

contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response (i.e. generation of an antibody that binds to a given epitope) can only be identified empirically (Greenspan et al. 1999 Nature Biotechnology 17: 936-937). The art does not teach any antibodies that bind to cyclopholin A to treat a Chlamydia infection. This constitutes undue experimentation. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of the art is unpredictable to antibodies that can bind to cyclophilin A to treat infection and have limitations with regard to complex life cycle of Chlamydia, the unknown mechanism of elementary bodies entering into the cell, the unknown signals whereby reticulate bodies reconvert to elementary bodies and the limitations of the treatments of administering antibodies to a subject.

Guidance in the specification. The specification fails to describe immunoepitopes against which the claimed antibodies are raised and must subsequently bind. The specification is silent as to what specific "immunoepitope" meets the limitations of the claims. Additionally, the specification is silent with regard to what epitopes are cross-reactive. There is no showing in the specification that the antibody that binds to cyclophilin A can be used to treat Chlamydia infection. The only information regarding antibodies is that they are capable of binding and they have the ability to block Chlamydia infection. The specification has not shown any antibodies that are specific for cyclophilin A to target cells infected with Chlamydia nor has the specification shown any cell surface receptors for Chlamydia that would bind to cyclophilin A. There is not empirical data reported on the specification at the time of filing showing efficacy of a therapeutic agent (i.e. antibody that binds specifically to cyclophilin A). Therefore the specification fails to describe any antibodies that specifically bind to cyclophilin A in the treatment of a Chlamydia infection.

Working examples. The specification does not give any working example (i.e. challenged mice models or passive immunization approaches).

In conclusion, the claimed inventions are not enabled for a method of treating a Chlamydia infection in a subject, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that disrupts the interaction between cyclophilin between cyclophilin and a cyclophilin binding partner. The claim is directed all antibodies with specificity to cyclophilin A. The state of the art teaches that although it *Chlamydia trachomatis* have a MIP (macrophage infectivity potentiator) like protein that posses peptidyl-prolyl cis-trans isomerase activity which is identical to cyclophilins like protein, it is poorly exposed. The state of the art teaches that the best approach for controlling the spread of chlamydial infection is vaccination, which have proved to have limitations. Furthermore the state of the art is unpredictable and does not teach any antibodies that bind to cyclophilin A to treat a Chlamydia infection. There is a lack of working examples. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Status of the Claims

5. No claims allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
GAU 1645
REM 3B31

MARK NAVARRO
PRIMARY EXAMINER